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Effects of adrenergic stimulation on sciatic nerve blood flow in diabetic and control rats

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Abstract

Sciatic endoneurial blood flow is reduced in experimental diabetes. This study examined the possible involvement of noradrenergic mechanisms in this impairment. In anaesthetised rats (pentobarbitone sodium 50 mg/kg, diazepam 2 mg/kg), sciatic nerve laser Doppler flux and vascular resistance in diabetic rats (5–6 weeks) were lower (approximately 50%) and higher (approximately 42%), respectively, than that in age-matched control rats, indicating nerve ischaemia in the diabetic tissues. Tyramine (1 nmol), noradrenaline (0.001–1 nmol) and phenylephrine (0.01–10 nmol) produced significant increases of nerve vascular resistance in control rats. The responses to tyramine (1 nmol) were completely blocked by desipramine (10 nmol) and those to phenylephrine (10 nmol) were reversed by phentolamine (1 nmol). In streptozotocin-diabetic rats, responses to phenylephrine or noradrenaline were enhanced compared to control rats, but the enhancement failed to reach statistical significance. The findings demonstrate that adrenergic stimulation affects sciatic nerve endoneurial blood flow. © 1997 Elsevier Science B.V.

Keywords: Adrenergic nerve; Diabetes mellitus; Nerve blood flow; Noradrenaline; Sciatic nerve, rat

1. Introduction

Histochemical studies, demonstrating innervation of vasa nervorum by noradrenergic, serotonergic and peptidergic nerve fibers, suggest a role in control of endoneurial blood flow for these perivascular nerves (Appenzeller et al., 1984). Epineurial application of vasoactive agents, such as noradrenaline, prostaglandins and capsaicin produced changes in endoneurial blood flow as measured by hydrogen clearance from endoneurial blood supply (Zochodne and Low, 1990; Zochodne and Ho, 1991; Kihara and Low, 1995a). The mode of application of these agents in these studies produced concurrent changes in mean arterial pressure and nerve blood flow, precluding separation of systemic from endoneurial actions. The use of hydrogen clearance for nerve blood flow measurement has low temporal resolution, restricting investigation to alterations of steady state. Thus, in the present study we used a technique which allowed the delivery of drugs directly to the endoneurium with concomitant monitoring of nerve blood flow, a method sensitive to transients, to examine the effects of adrenergic stimulation of blood vessels supplying the rat sciatic nerve.

A vascular hypothesis for the aetiology of diabetic neuropathy suggests that endoneurial hypoxia derives from reduced peripheral nerve blood flow, with deleterious effects of hypoxia on nerve structure and function. In human clinical diabetic neuropathy, reduced sural nerve oxygen tension has been reported (Newrick et al., 1986). In experimental diabetes, reduced endoneurial blood flow associated with nerve dysfunction has been reported in rat sciatic nerves (Tuck et al., 1984; Stevens et al., 1994). We have previously reported that a deficit in nitric oxide production may be responsible for reduced nerve blood flow in diabetic rats (Omawari et al., 1996). The mechanism involved in this reduction is poorly understood, chiefly because the pharmacology of blood vessels supplying nerves is not well characterised. Thus in this study, using a novel technique for local delivery of drugs in the endoneurium, we investigated the influence of adrenergic stimulation on sciatic nerve blood flow in normal rats and examined the possible changes of these stimulations in diabetes mellitus, using streptozotocin-induced diabetic rats as a model.

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2. Materials and methods

2.1. Measurement of sciatic nerve blood flow

Male Wistar rats (350–450 g) were anaesthetised initially by intraperitoneal injection of pentobarbitone sodium (50 mg/kg) and diazepam (2 mg/kg). Anaesthesia was maintained by intravenous infusion of pentobarbitone sodium (15 mg/ml) and diazepam (0.5 mg/ml) at a rate of 50 μl/15 min via the jugular vein. The right carotid artery was cannulated for measurement of systemic arterial pressure by a pressure transducer (Type 4-327-L223, Bell and Howell, UK). The left sciatic nerve was exposed and nerve laser Doppler flux was measured using a fibre optic flow probe (diameter 800 μm, Type P4, Moors Instruments, UK), as an index of nerve blood flow, expressed in arbitrary units. The output from the pressure transducer was amplified via a MacLab Bridge Amp (AD Instruments, UK). The bridge amplifier and flow monitor outputs were digitised via a MacLab/8 Interface Module (AD Instruments), displayed and recorded simultaneously using MacLab Chart software (AD Instruments). Rat body temperature was maintained at 37.5 ± 0.5°C via homeothermic blanket, with biofeedback by rectal probe (Harvard Apparatus, UK).

2.2. Endoneurial drug administration

After establishing a steady-state sciatic nerve laser Doppler flux, drugs were delivered to the endoneurium as previously described by Omawari et al. (1996). Briefly, a volume (0.5 μl) of saline with/without the test drug was infused (over a 2-min period) into the endoneurium using a glass micropipette (tip diameter 10–15 μm) connected to a microdispenser (Laser Labs, UK), via a guide hole (300–350 μm diameter) punctated with an etched tungsten probe, 1–2 mm proximal to the laser Doppler probe. Serial administration of a test drug was delivered through the same guide hole 20–30 min apart, i.e. after the laser Doppler flux had stabilised or returned to the original baseline. Each sciatic nerve received one test drug only, except for desipramine, which was coinfused with tyramine, and phentolamine, which was infused at the end of the phenylephrine experimental protocol. All responses to test drugs were measured at steady-state conditions, usually 15 min after each injection and expressed as percentage change in neurovascular resistance corrected for mean arterial pressure, relative to the value recorded before each injection. In time-control experiments, physiological saline was used to demonstrate the transient effect of the local injection on baseline laser Doppler flux.

2.3. Induction of diabetes

In a separate set of experiments, male Wistar rats (300–350 g; Charles River, UK) were randomly separated into age-matched control and diabetic groups for each of the experiments in this study. Rats were weighed, fasted overnight and those from the designated group were made diabetic by a single injection of streptozotocin (50 mg/kg, i.p.) dissolved immediately before injection in sterile physiological saline. Food and water were allowed ad libitum to all animals. Forty-eight hours after injection, blood samples were obtained by tail prick and glucose levels were determined using strip-operated reflectance photometry (Reflolux, Boehringer-Mannheim, UK). Rats with blood glucose levels less than 15 mM were excluded from the study.

Animals were weighed weekly and used for experimentation at the end of 5–6 weeks of diabetes. Endoneurial administration of specified drugs with concomitant monitoring of sciatic nerve laser Doppler flux was carried out as described above. At the conclusion of an experiment, blood samples were collected via the abdominal aorta, in heparinized syringes, centrifuged and plasma stored in Eppendorf tubes at −4°C until assay for glucose levels by spectrophotometry (GOD-PERID test; Boehringer Mannheim).

2.4. Drugs

All drugs were obtained from Sigma (UK), except for pentobarbitone sodium (May and Baker, UK) and diazepam (Dumex, UK). Drugs were dissolved in physiological saline (0.9% sodium chloride) on the day of use.

2.5. Statistical analysis

All data were expressed as mean ± 1 S.D. and analysed by one- or two-way analysis of variance (ANOVA), followed by Student-Newman-Keuls test, or Student's *t*-test where appropriate. $P < 0.05$ was taken as statistical significance between groups.

3. Results

3.1. Assessment of diabetes

Successful induction of diabetes was confirmed by significant increases in plasma glucose levels in streptozotocin-diabetic rats (41.3 ± 5.9 mM, $n = 36$) compared to control rats (9.6 ± 0.9 mM, $n = 32$; $P < 0.05$, unpaired Student's *t*-test). Diabetic rats also had significantly lower final body weights than age-matched controls (300 ± 61 g, $n = 36$ vs. 443 ± 100 g, $n = 34$; $P < 0.05$, unpaired Student's *t*-test). Rats injected with streptozotocin were also polyuric and polydipsic.

3.2. Sciatic nerve blood flow

The sciatic nerve blood flow (arbitrary units) and vascular resistance (mmHg/Doppler units) recorded from the

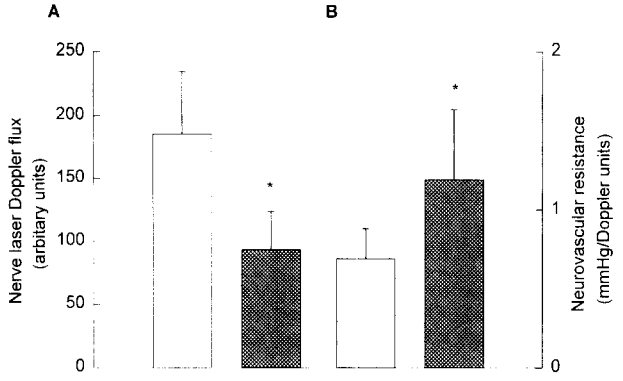

Fig. 1. (A) Laser Doppler flux and (B) vascular resistance in sciatic nerves from control (open bars; $n = 34$) and streptozotocin-diabetic (cross-hatch bars; $n = 36$) rats. Neurovascular resistance was calculated from mean arterial systemic pressure (mmHg) corrected for nerve laser Doppler flux (arbitrary units). * Significant difference from control, $P < 0.05$, unpaired Student's t-test. Values are arithmetic mean + 1 S.D.

streptozotocin-diabetic group were significantly lower and higher, respectively, than that of the age-matched control group (Fig. 1; $P < 0.05$, unpaired Student's t-test). To eliminate possible influences of differences between control and diabetic rats in mean systemic arterial pressure, all nerve Doppler data are calculated as nerve vascular resistance and expressed as percentage change relative to pre-treatment levels.

3.3. Influence of adrenergic stimulation on sciatic nerve blood flow

Endoneurial infusion of noradrenaline (1 nmol) caused severe depression of nerve laser Doppler flux without affecting the systemic arterial pressure (Fig. 2). Fig. 3A shows group mean data for the increase in nerve vascular resistance with cumulative doses of noradrenaline (0.001–1 nmol). When equi-volumes of the vehicle (saline) were used instead of noradrenaline, there were no significant changes in nerve vascular resistance (Fig. 3A). In streptozotocin-diabetic rats, the responses to noradrenaline were more pronounced than in control rats; however, the apparent differences failed to reach statistical significance (Fig. 3B; $P > 0.05$, two-way ANOVA). Similarly, endoneurial infusion of phenylephrine (0.01–10 nmol) caused increases in neurovascular resistance (Fig. 3C), with a trend of an enhancement in streptozotocin-diabetic rats. The responses in streptozotocin-diabetic rats were not significantly different from that in control rats (Fig. 3C; $P > 0.05$, two-way ANOVA). Phentolamine (1 nmol) completely reversed the responses to 10 nmol phenylephrine (Table 1).

When infused separately, phentolamine had no effect on nerve vascular resistance at the low doses (0.1–10 fmol), but higher doses (100–1000 fmol) caused increases in nerve vascular resistance in control rats (Fig. 4A). In

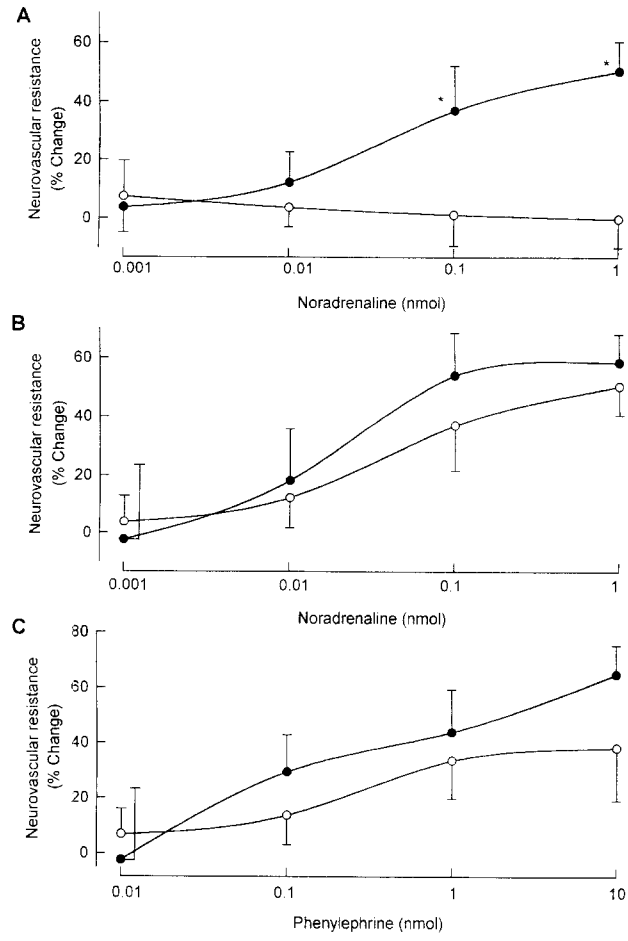

Fig. 3. (A) The effect of noradrenaline (●) on sciatic nerve vascular resistance in normal rats. In time-control experiments, vehicle (0.5 μl saline, ○) was used. Responses to cumulative doses of (B) noradrenaline and (C) phenylephrine in sciatic nerve vasculature from control (○) and streptozotocin-diabetic (●) rats. * Significant difference from corresponding saline control, $P < 0.05$, two-way ANOVA, followed by multiple comparison using Student-Newman-Keuls test. Values are arithmetic mean ± 1 S.D. from 5–8 preparations.

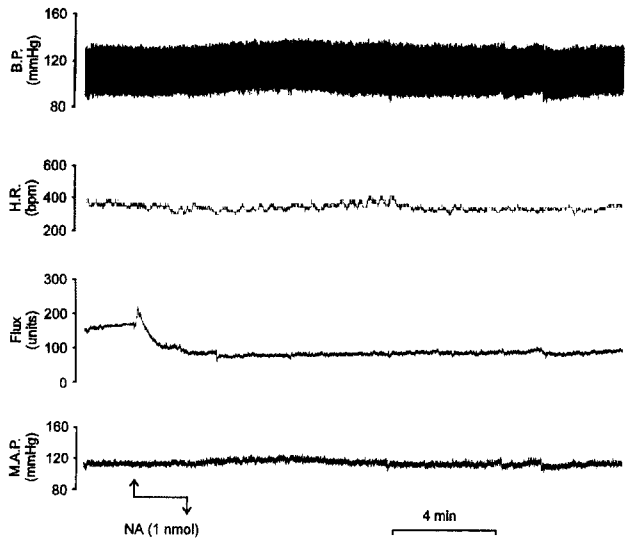

Fig. 2. The original trace shows the effect of noradrenaline (NA) on sciatic nerve laser Doppler flux, systemic arterial pressure and heart rate.

Table 1
Changes in sciatic nerve blood flow before and after phenylephrine and the reversal effect of phentolamine on phenylephrine-induced response in control rats

	Sciatic nerve laser Doppler flux (arbitrary units)	
	Before	After
Phenylephrine – 10 nmol (5)	179.7 ± 56.1	108.2 ± 36.8 [a]
Phentolamine – 1 nmol (3)	112.0 ± 24.1	178.1 ± 33.7 [a]

Data are arithmetic mean ± 1 S.D. from the number of preparations indicated in parentheses. Phentolamine was infused into the endoneurium once the response to phenylephrine had reached steady state (15 min), and the reversal effect of phentolamine was measured 10 min after its infusion.
[a] Significant difference from before responses, $P < 0.05$, paired Student's t-test.

Table 2
The effect of tyramine (1 nmol), in the absence and presence of desipramine (10 nmol), on sciatic nerve vascular resistance in control and streptozotocin (STZ)-diabetic rats

	Neurovascular resistance (% change)	
	Control	STZ-diabetic
Tyramine	45.8 ± 17.2 (6)	53.2 ± 12.7 (6)
Tyramine + desipramine	– 2.62 ± 12.3 (4) [a]	ND

Data are calculated as nerve vascular resistance (% change) and expressed as percentage change relative to pre-treatment levels. Group data are mean ± 1 S.D. from the number of preparations indicated in parentheses. In separate preparations, desipramine was coinjected with tyramine. ND denotes not done in streptozotocin-diabetic rats.
[a] Significant difference from tyramine alone from the control group, $P < 0.05$, one-way ANOVA.

streptozotocin-diabetic rats, phentolamine at the lower doses produced a decrease in nerve vascular resistance; the response to 0.1 pmol phentolamine was significantly different from those in control rats (Fig. 4A; $P < 0.05$, two-way ANOVA).

Tyramine at a dose of 1 nmol produced a similar, marked increase of vascular resistance in sciatic nerves from both control and streptozotocin-diabetic rats (Table 2); the effect was prevented by co-injection of desipramine (10 nmol).

At lower doses (0.001–0.01 nmol) isoprenaline produced decreases, but at higher doses (0.1–1 nmol) produced small increases in sciatic nerve vascular resistance from normal rats (Fig. 4B). The response to the lowest dose of isoprenaline (0.001 nmol) in the diabetic group was significantly different from that in control group ($P < 0.05$, two-way ANOVA).

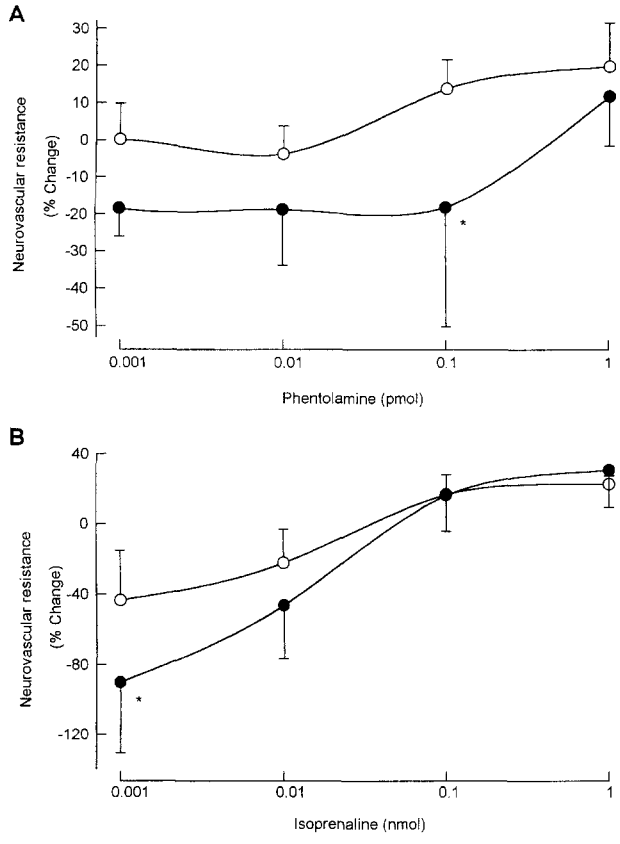

Fig. 4. The effect of cumulative doses of (A) phentolamine and (B) isoprenaline on sciatic nerve vasculature from control (○) and streptozotocin-diabetic (●) rats. * Significant difference from corresponding control, $P < 0.05$, two-way ANOVA, followed by multiple comparison using Student-Newman-Keuls test. Values are arithmetic mean ± 1 S.D. from 4–6 preparations.

4. Discussion

The present study examined the influence of stimulation of adrenoceptors on sciatic nerve blood flow in control and streptozotocin-diabetic rats. The application of adrenoceptor stimulant drugs directly into the endoneurium alters nerve blood flow as measured by laser Doppler flux. A major advantage of using this technique is that the direct delivery of drugs to the endoneurium was devoid of spillover effect on the systemic circulation, unlike that observed with topical application used in previous reports (Low et al., 1989; Zochodne and Low, 1990). However, it is uncertain how the test drugs are distributed within the endoneurial compartment. As stated in our previous report (Omawari et al., 1996), pilot studies show that injected dye diffuses slowly away from the pipette tip and distributes evenly throughout the endoneurium, without leakage to the epineurium.

Endoneurial infusions of tyramine produced a marked depression of nerve blood flow, providing indirect evidence for a possible presence of noradrenergic nerve terminals innervating blood vessels supplying the endoneurium. The vasoconstrictor effect of tyramine was blocked by the neuronal uptake blocker desipramine, confirming the indirect sympathomimetic action of tyramine on adrenergic nerve terminals via the neuronal uptake system. However, these findings do not exclude the possibility of another

source of noradrenaline, which is independent of blood vessels, i.e. the intrafascicular adrenergic nerves histochemically shown by Dhital et al. (1986). It is not known whether these nerves are associated endoneurial blood vessels. These microvessels have been found to consist of arterioles, venules and capillaries (Bell and Weddell, 1984). The arterioles are thin-walled with rudimentary internal elastic laminae, the capillaries are nonfenestrated and continuous with prominent, often multiple basal laminae, and are enclosed by possibly contractile pericytes. Any of these blood vessels could be responsive to administered drugs.

Noradrenaline caused dose-dependent reductions in sciatic nerve blood flow without affecting systemic arterial pressure (Fig. 2), indicating further the possible presence of functional postsynaptic adrenoceptors. Similarly, phenylephrine produced the same effect as noradrenaline, its action was reversed by the α-adrenoceptor antagonist phentolamine, indicating that phenylephrine was acting through α-adrenoceptors. The findings are in accordance with reports by others, who found that epineurial noradrenaline decreased nerve blood flow in a dose-dependent manner and that its action was sensitive to phentolamine (Zochodne and Low, 1990; Kihara and Low, 1990; Van Buren et al., 1996). In the present study, application of low doses of phentolamine alone had no significant effect on nerve vascular resistance, implying that stimulation of α-adrenoceptors has only a limited influence on endoneurial blood flow under basal conditions. However, at higher doses phentolamine produced increases in nerve vascular resistance, perhaps by promoting noradrenaline release via presynaptic receptor inhibition.

Isoprenaline at low doses decreased nerve vascular resistance, possibly acting through vasodilatory β-adrenoceptors on smooth muscle. Interestingly, at higher doses isoprenaline produced small decreases in nerve blood flow. The mechanism for this effect is not clear. We considered the possible involvement of stimulation of presynaptic β-adrenoceptors with resulting increases in noradrenaline release, but it is difficult to envisage such an effect overcoming the direct vasodilator action of isoprenaline. Further experiments are required to elucidate the subtype of β-adrenoceptors involved.

As previously reported from our laboratory (Stevens et al., 1994; Omawari et al., 1996) and as well as in the present study, sciatic nerve blood flow was reduced in streptozotocin-diabetic rats compared to age-matched controls. A similar reduction in sciatic nerve blood flow in diabetic rats has been reported by other investigators using a same or a different method of measuring nerve blood flow and these reductions have been shown to be associated with reduced nerve conduction velocity (Tuck et al., 1984; Cameron et al., 1991; Zochodne et al., 1992; Kihara and Low, 1995b; Van Buren et al., 1996). The ischaemia was reversed by a parallel treatment of diabetic rats with insulin (Stevens et al., 1994). These data support the proposal that endoneurial hypoxia may contribute to nerve dysfunction associated with diabetes in animals (Tomlinson, 1992; Cameron and Cotter, 1994) and diabetic peripheral neuropathy in humans (Newrick et al., 1986).

In the present study, responses to stimulation of adrenoceptors by noradrenaline and phenylephrine were more pronounced in sciatic nerves from diabetic rats than in control rats, suggesting, perhaps, a general hyper-responsiveness to adrenoceptor agonists in diabetic tissues. In consideration of the complex interplay of systemic and local presynaptic and postsynaptic processes in the regulation of nerve blood flow in vivo, it is difficult to draw definitive conclusions on aspects of the adrenergic contribution to nerve blood flow ischaemia in diabetes, based on the altered trends of responsiveness to the above adrenergic agonists. However, in other studies a hypersensitivity to noradrenaline superfusion has been showed in laser Doppler monitored vascular resistance of sciatic nerve epi/perineurial vessels (Cameron and Cotter, 1994). A modest involvement of exaggerated noradrenergic vasoconstrictor tone in endoneurial ischaemia in diabetic rats is also supported by the observation that treatment of diabetic rats with guanethidine returned nerve blood flow and conduction velocity within normal ranges (Cameron et al., 1991). In contrast, Van Buren et al. (1996) reported a hyposensitivity to noradrenergic stimulation by phenylephrine and tyramine. The reason for the discrepancy may relate to the longer duration of diabetes (12 weeks) used in the latter study and that drugs were indirectly delivered to the sciatic nerve via the common iliac artery. The similar responses to tyramine in diabetic and control groups may imply a differential effect of diabetes on the release of noradrenaline or nerve degeneration. The mean density of adrenergic nerve fibers in the endoneurium of the tibial nerve from diabetic rats is lowered at 5 weeks after streptozotocin (Koistinaho et al., 1990).

A recently proposed mechanism for vascular dysfunction in diabetes involved reduced production or availability of vasodilators such as nitric oxide or prostacyclin, and perhaps with a concomitant increased sensitivity to vasoconstrictors such as noradrenaline (Ward et al., 1989; for review, see Tomlinson et al., 1992; Cameron and Cotter, 1994). A 30-fold increased sensitivity to noradrenaline in epi/perineurial vessels from diabetic rats was normalised by the presence of a nitric oxide synthase inhibitor, showing a marked deficit in nitric oxide release or production which may be responsible for the hypersensitivity to noradrenaline (Cameron and Cotter, 1994). Recently, we reported a possible deficit of nitric oxide production in the sciatic nerve endoneurial blood vessels (Omawari et al., 1996). Yet, it is to be determined whether this deficit may, at least in part, account for the hyper-responsiveness to adrenoceptor stimulation reported in the present study.

In conclusion, the present data demonstrate the influence of adrenergic stimulation on endoneurial blood flow of the rat sciatic nerve. However, further studies are necessary to elucidate the possible alterations in response

to adrenergic stimuli in diabetes and their involvement in the deficit nerve blood flow associated with this disease state.

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References

Appenzeller, O., Dhital, K.K., Cowen, T., Burnstock, G., 1984. The nerves to blood vessels supplying blood to nerves: the innervation of vasa nervorum. Brain Res. 304, 383–386.

Bell, M.A., Weddell, A.G.M., 1984. A descriptive study of the blood vessels of the sciatic nerve in the rat, man and other mammals. Brain 107, 871–898.

Cameron, N.E., Cotter, M.A., 1994. The relationship of vascular changes to metabolic factors in diabetes mellitus and their role in the development of peripheral nerve complications. Diabetes Metab. Rev. 10, 189–224.

Cameron, N.E., Cotter, M.A., Low, P.A., 1991. Nerve blood flow in early experimental diabetes in rats: relation to conduction deficits. Am. J. Physiol. 261, E1–E8.

Dhital, K., Lincoln, J., Appenzeller, O., Burnstock, G., 1986. Adrenergic innervation of vasa and nervi nervorum of optic, sciatic, vagus and sympathetic nerve trunks in normal and streptozotocin-diabetic rats. Brain Res. 367, 39–44.

Kihara, M., Low, P.A., 1990. Regulation of rat nerve blood flow: role of epineurial alpha-receptors. J. Physiol. 422, 145–152.

Kihara, M., Low, P.A., 1995a. Vasoreactivity to prostaglandins of rat peripheral nerve. J. Physiol. 484, 463–467.

Kihara, M., Low, P.A., 1995b. Impaired vasoreactivity to nitric oxide in experimental diabetic neuropathy. Exp. Neurol. 132, 180–185.

Koistinaho, J., Wadhwani, K.C., Rapoport, S.I., 1990. Adrenergic innervation in the tibial and vagus nerves of rats with streptozotocin-induced diabetes. Brain Res. 513, 106–112.

Low, P.A., Lagerlund, T.D., McManis, P.G., 1989. Nerve blood flow and oxygen delivery in normal, diabetic and ischemic neuropathy. Int. Rev. Neurobiol. 31, 355–438.

Newrick, P.G., Wilson, A.J., Jakubowski, J.A., Boulton, A.J.M., Ward, J.D., 1986. Sural nerve oxygen tension in diabetes. Br. Med. J. 293, 1053–1054.

Omawari, N., Dewhurst, M., Vo, P.A., Mahmood, S., Stevens, E., Tomlinson, D.R., 1996. Deficient nitric oxide responsible for reduced nerve blood flow in diabetic rats: effects of L-NAME, L-arginine, sodium nitroprusside and evening primrose oil. Br. J. Pharmacol. 118, 186–190.

Stevens, E.J., Carrington, A.L., Tomlinson, D.R., 1994. Nerve ischaemia in diabetic rats: time-course of development, effect of insulin treatment plus comparison of streptozotocin and BB models. Diabetologia 37, 43–48.

Tomlinson, D.R., 1992. The pharmacology of diabetic neuropathy. Diabetes Metab. Rev. 7, 67–84.

Tomlinson, K.C., Gardiner, S.M., Hebden, R.A., Bennett, T., 1992. Functional consequences of streptozotocin-induced diabetes mellitus, with particular reference to the cardiovascular system. Pharmacol. Res. 44, 103–150.

Tuck, R.R., Schmelzer, J.D., Low, P.A., 1984. Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy. Brain 107, 935–950.

Van Buren, T., Kasbergen, C.M., Gispen, W.H., De Wildt, D.J., 1996. Presynaptic deficit of sympathetic nerves: a cause for disturbed sciatic nerve blood flow responsiveness in diabetic rats. Eur. J. Pharmacol. 296, 277–283.

Ward, K.K., Low, P.A., Schmelzer, J.D., Zochodne, D.W., 1989. Prostacyclin and noradrenaline in peripheral nerve of chronic experimental diabetes in rats. Brain 112, 197–208.

Zochodne, D.W., Ho, L.T., 1991. Influence of perivascular peptides on endoneurial blood flow and microvascular resistance in the sciatic nerve of the rat. J. Physiol. 444, 615–630.

Zochodne, D.W., Low, P.A., 1990. Adrenergic control of nerve blood flow. Exp. Neurol. 109, 300–307.

Zochodne, D.W., Ho, L.T., Gross, P.M., 1992. Acute endoneurial ischemia induced by epineurial endothelin in the rat sciatic nerve. Am. J. Physiol. 263, H1806–H1810.